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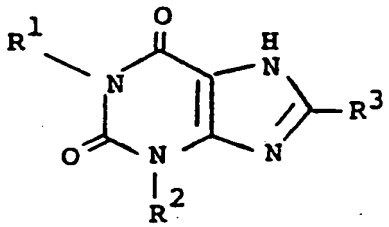
(54) Xanthinederivatives, process for their preparation and their pharmaceutical use.

(57) A method for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or other disorders which method comprises the administration of an effective, non-toxic amount of a compound of formula (I):



(I)

or if appropriate a pharmaceutically acceptabl salt thereof, wherein R^1 and R^2 each independently r present alkyl or a moiety of formula (a):

$-(CH_2)_m-A$ (a)

wherein m r presents zero or an integ r 1, 2 or 3;
A represents a substituted or unsubstituted cyclic hydrocarbon radical; and
R^3 represents a halogen atom, a nitro group, or a group $-NR^4R^5$ wherein R^4 and R^5 each independently represents hydrogen, alkyl or alkylcarbonyl or R^4 and R^5 together with the nitrogen to which they are

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TREATMENT AND COMPOUNDS

The present invention relates to a novel method of treatment and to certain novel compounds having pharmacological activity, to a process for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

Molecular Pharmacology, Volume 6, No. 6, 1970, p.597-603 discloses 1,3-dimethyl-8-nitro-xanthine. This compound is disclosed as having lipolytic activity.

Annalen der Chemie, 47, 362-365 (1957) discloses 1,3-dimethyl-8-amino-xanthine and a process by which it may be prepared. No pharmacological utility is disclosed for this compound.

Drug Res. 27(1) Nr 19, 1977, pages 4-14, Van K.H. Klingler discloses certain 1,3-dimethyl- 8-substituted xanthines as intermediates solely in the synthesis of phenylethyl aminoalkyl xanthines.

Drug Res. 31 (11), Nr. 12, 1981, R.G. Werner et al, pages 2044-2048 discloses certain 1,3-dimethyl-8-substituted xanthines. No pharmacological activity is disclosed for these compounds.

It has now been discovered that certain 8-substituted xanthines have a protective effect against the consequences of cerebral metabolic inhibition. The said compounds improve data acquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated with Parkinson's disease.

These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the compound is indicated to be of benefit for the treatment of functional disorders resulting from disturbed brain function following ischaemia.

These compounds are also active in increasing the oxygen tension in ischaemic skeletal muscle. This property results in an increase in the nutritional blood flow through ischaemic skeletal muscle which in turn indicates that the compounds of the invention are of potential use as agents for the treatment of peripheral vascular disease such as intermittent claudication.

These compounds also act as phosphodiesterase inhibitors and elevate cyclic AMP levels and are therefore of potential use in the treatment of proliferative skin disease in human or non-human mammals.

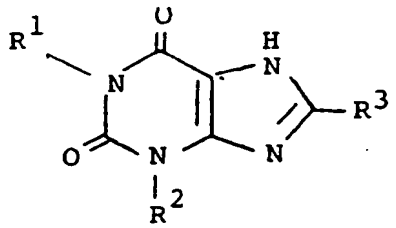
These compounds are also indicated to have bronchodilator activity and thus to be of potential use in the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma.

It has now also surprisingly been discovered that these compounds are good inhibitors of induced blood eosinophilia and that they are therefore potentially useful in the treatment and/or prophylaxis of disorders associated with increased numbers of eosinophils, such as asthma, and allergic disorders associated with atopy, such as urticaria, eczema and rhinitis.

Certain of the novel compounds are also indicated to possess useful adenosine A1 antagonist activity.

Finally the present compounds also show good metabolic stability.

Accordingly, the invention provides a method for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin disease and/or for disorders of the respiratory tract and/or the treatment or prophylaxis of disorders associated with increased numbers of eosinophils and allergic disorders associated with atopy, which method comprises the administration of an effective, non-toxic amount of a compound of formula (I):



(I)

or if appropriate a pharmac utically acceptable salt thereof, wherein R^1 and R^2 each independently represent alkyl or a moiety of formula (a):

tyl or cyclohexyl group.

Favourably, A represents a cyclopropyl group or a cyclobutyl group.

Preferably, A represents a cyclopropyl group.

When R^1 or R^2 represents alkyl, a preferred alkyl group is an n-butyl group.

An example of R^3 or R^{3a} includes a nitro group or a group $-NHR^4$ wherein R^4 represents hydrogen or alkylcarbonyl.

When R^3 or R^{3a} represents a halogen atom it is suitably a bromine or a chlorine atom.

When either of R^4 or R^5 represents alkyl or alkylcarbonyl, it is preferred if the other of R^4 or R^5 represents hydrogen.

An example of an alkylcarbonyl group is an acetyl group.

Suitable heterocyclic groups include saturated or unsaturated heterocyclic groups having single or fused rings, each ring having 5 to 7 ring atoms which ring atoms optionally comprise up to two additional hetero atoms selected from O, N or S.

Favoured heterocyclic groups include rings comprising 5 to 7, especially 5 or 6 and preferably 6, ring atoms.

Favoured additional hetero atoms are O or N, especially O.

Favoured heterocyclic groups are saturated heterocyclic groups.

Favoured heterocyclic groups are single ring heterocyclic groups.

Favoured heterocyclic groups comprising 5 ring atoms include pyrrolidinyl groups.

Favoured heterocyclic groups comprising 6 ring atoms include piperidinyl or morpholinyl groups.

Suitably, R^3 represents amino.

Suitably, R^{3a} represents amino.

Suitably, m represents zero or the integer 1.

Favourably, m represents 1.

Suitable pharmaceutically acceptable salts are pharmaceutically acceptable base salts and pharmaceutically acceptable acid addition salts. Generally compounds of formula (I) wherein R^3 is nitro form base salts, suitable pharmaceutically acceptable base salts of the compounds of formula (I) include 7-N base salts including metal salts, such as alkali metal salts for example sodium salts, or organic amine salts such as that provided with ethylenediamine.

Certain of the compounds of formula (I) wherein R^3 is amino form acid addition salts, suitable acid addition salts of the compounds of formula (I) are the acid addition salts including pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphate, α-keto glutarate, α-glycerophosphate and glucose-1-phosphate. Preferably the acid addition salt is a hydrochloride salt.

The pharmaceutically acceptable salts of the compounds of formula (I) are prepared using conventional procedures.

A suitable compound of formula (I) is a compound of formula (IA).

When used herein the term 'cyclic hydrocarbon radical' includes single ring and fused ring, cyclic hydrocarbons comprising up to 8 carbon atoms in each ring, suitably up to 6 carbon atoms, for example 3, 4, 5 or 6 carbon atoms.

Suitable optional substituents for any cyclic hydrocarbon radical includes a C_{1-6} alkyl group or a halogen atom.

When used herein the term 'alkyl' whether used alone or when used as part of another group (for example as in an alkylcarbonyl group) includes straight and branched chain alkyl groups, containing from 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms, for example methyl, ethyl, propyl or butyl.

When used herein the expression 'proliferative skin diseases' means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases include: psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non-malignant keratosis, acne, and seborrheic dermatitis in humans and atopic dermatitis and mange in domesticated animals.

The compounds of formula (I) ar preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material consider d toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

A^1 is -NH.CHO then A^2 is NH_2; and thereafter, if required, converting any group R^{1a} to R^1 and/or R^{2a} to R^2. The dehydrating cyclisation of a compound of formula (III) may be carried out under any suitable conditions. Favourably the conditions chosen are these wherein the water formed is removed from the reaction mixture, thus the reaction is generally carried out at an elevated temperature in the range of from 100°C to 200°C, such as in the range of 180°C to 190°C.

In one aspect of the process, especially when A^1 is -NO and A^2 is $-NH.CH_3$, the reaction is carried out in a solvent immiscible with water, such as toluene, at the reflux temperature of the solvent, the water being removed using a water-separator.

Suitable values for R^{1a} and R^{2a} include R^1 and R^2 respectively or nitrogen protecting groups such as benzyl groups.

When R^{1a} or R^{2a} represents other than R^1 or R^2 repectively, the abovementioned conversions of R^{1a} into R^1 and R^{2a} to R^2 may be carried out using the appropriate conventional procedure. For example when R^{1a} (or R^{2a}) represents a nitrogen protecting group, such as a benzyl group, the protecting group may be removed using the appropriate conventional procedure, such as catalytic hydrogenation, and the resulting product reacted with a compound of formula (IV):

$X\text{-}(CH_2)_m\text{-}A$ (IV)

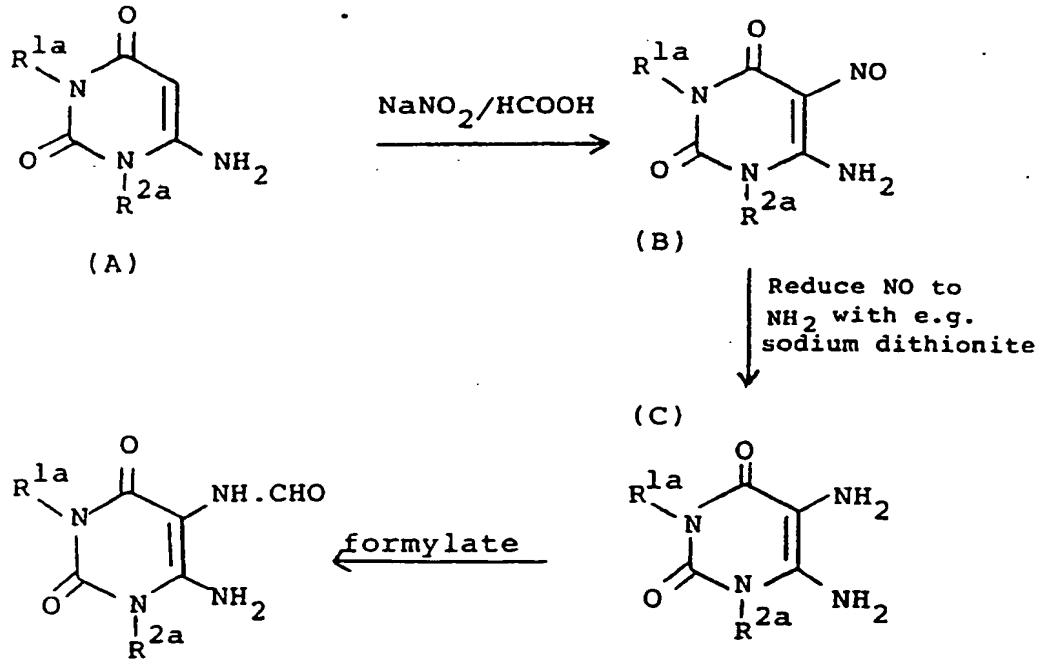
wherein A and m are as defined in relation to formula (IA) and X represents a leaving group, such as halide, for example bromide or iodide.

The protection of any reactive group or atom, such as the xanthine nitrogen atom may be carried out at any appropriate stage in the aforementioned process. Suitable protecting groups include those used conventionally in the art for the particular group or atom being protected, for example suitable protecting groups for the xanthine nitrogen atoms are benzyl groups.

Protecting groups may be prepared and removed using the appropriate conventional procedure:

For example, N-benzyl protecting groups may be prepared by treating the appropriate compound of formula (II) with benzyl chloride in the presence of a base such as triethylamine. The N-benzyl protecting groups may be removed by catalytic hydrogenation over a suitable catalyst, such as palladium on activated charcoal, in a suitable solvent, such as ethanol conveniently at an elevated temperature, or by treatment with anhydrous aluminium chloride in dry benzene at ambient temperature.

A compound of formula (III) wherein A^1 represents -NH.CHO and R^2 represents $-NH_2$ may suitably be prepared from a 6-aminouracil of formula (A) according to the following reaction scheme:



wherein R^{1a} and R^{2a} are as defined in relation to formula (II).

Suitably, the reaction conditions used in the abovementioned reaction scheme are appropriate conven-

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wherein R^{4b} and R^{5b} are as defined above.

The reaction between the compound of formula (IA) and the compound of formula (III) may be carried out in any suitable solvent, such as toluene, at any temperature providing a convenient rate of formation of the product, but suitably at an elevated temperature, such as in the range of from 50° to 180°C, at atmospheric or an elevated pressure.

Suitable alkylation methods for use in the abovementioned conversions include those used conventionally in the art, for example methods using halides, preferably iodides, in the presence of a base such as potassium carbonate in any convenient solvent for example acetonitrile or toluene.

Suitable acylation methods for use in the abovementioned conversions include those used conventionally in the art, thus an amino group may be converted into an alkylcarbonyl amino group by using an appropriate acylating agent, for example an amino group may be converted to an acetylamino group by using acetic anhydride at elevated temperature.

The compounds of formula (I) may be prepared according to the abovementioned methods or, as appropriate, by the methods of the abovementioned publications.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, such as from 0.1 to 50 microns, preferably less than 10 microns, for example from 1 to 10 microns, 1 to 5 microns or from 2 to 5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators, for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; xanthine derivatives such as theophylline and aminophylline and corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the conc ntration used, can be eith r susp nded or dissolved in the vehicle. In pr paring solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitabl vial or ampoule and sealing. Advantageously, adjuvants such as a local ana sthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead

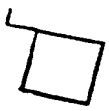
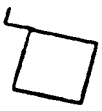
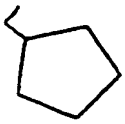
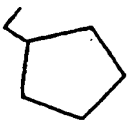
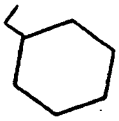
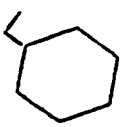
The separated organic layer was then dried over anhydrous sodium sulphate and concentrated in vacuo. The product crystallized from the concentrate to yield a yellow crystalline product yield 12.2g, (56.5%), m.pt. 207° C (with decomposition).

^{1}H NMR ($CDCl_3$):

ppm: 0.35-0.7 (m, 8H), 1.1 -1.7 (m, 2H), 3.95-4.2 (m, 4H), 9.0-11.0 (br exchanges with D_2O, 1H).

The following compounds were prepared using an analogous procedure to that described in Example 1. The appropriate 1,3-di-cycloalkylmethyl xanthine substrates were prepared according to the procedures described herein in and in United Kingdom Patent Application No. 8826595.4.

Table 1

Ex. No	R^1	R^2	R^3	M.pt (°C)	^{1}H NMR Spectrum: ($CDCl_3$ or $CDCl_3$/DMSO, ppm)
3			NO_2	220	1.7-2.2 (m, 12H) 2.5-3.1 (m, 2H) 4.1-4.3 (m, 4H)
4			NO_2	148-150	1.1 -2.0 (m, 16H) 2.15-2.7 (m, 2H) 4.15 (d, J=7.7Hz, 4H)
5			NO_2	140	0.75-2.2 (m, 22H) 3.7 -4.1 (m, 4H)
6			NO_2	>250	0.7 -1.4 (m, 8H) 2.5 -3.4 (m, 2H)

Example 7

1,3-Di-n-butyl-8-amino xanthine hydrochloride

1,3-Di-n-butyl-8-nitro xanthine from Example 1 (8.5g) was suspended in concentrated hydrochloric acid (85ml) and then treated at room temperature with tin powder (14.5g) in small portions. After stirring for 10 minutes the yellow colour of the suspension disappeared. Thereafter the precipitate was filtered off and recrystallised twice from ethanol. The product formed colourless crystals, yield 5.5g (63%) m.pt>250° C

^{1}H NMR (DMSO):

ppm: 0.90 (t, J=6.1Hz, 6H), 1.05-1.9 (m, 8H), 3.65-4.15 (m, 4H), 6.9 (br, exchanges with D_2O, 4H).

Example 8

1,3-Di-n-butyl-8-amino xanthine

Neutralisation of the hydrochloride from Example 6 with 1N sodium hydroxide solution gave the 1,3-di-

hours the solvent was removed in vacuo, the residue taken up with dichloromethane and extracted with water (40ml).

After drying the organic layer over anhydrous sodium sulphate, the solvent was removed and the residue crystallised from ethanol, yield 0.06g (17%), m.pt. >250° C.

^{1}H NMR ($CDCl_3$):
ppm: 0.6-1.4 (m, 8H), 2.6-3.25 (m,2H), 7.8 (s, 1H), 12 (br. exchanges with D_2O, 1H).

Example 14

1,3-Di-n-butyl-8-acetamido xanthine

1.3-Di-n-butyl-8-amino xanthine (0.5g), hydrochloride in toluene (30ml) was stirred for 30 minutes with triethylamine (0.16g). After addition of acetic anhydride (0.32g), the mixture was refluxed for 6 hours. The reaction mixture was extracted with water (4 x 30ml), the organic layer separated and dried over anhydrous sodium sulphate. The solvent was then evaporated to yield the product, yield 0.1g (20%), mpt. 180° C.
^{1}H NMR ($CDCl_3$):
ppm: 0.93 (t, J=6.4Hz, 6H), 1.1-1.9 (m, 8H), 2.27 (s, 3H), 4.01 (t, J=6.7Hz), 8.9 (br, exchanges with D_2O, 1H).

Example 15

1,3-Di-n-butyl-8-chloro xanthine

1,3-Di-n-butyl-8-nitro xanthine (0.5g, 0.0016mol) was refluxed for 18 hours with concentrated hydrochloric acid (8ml). The reaction mixture was extracted with dichloromethane (20ml), the organic layer washed with water to neutrality and then dried over anhydrous sodium sulphate. The solvent was then removed by evaporation in vacuo and the residue was recrystallised from ethanol, to give the title compound, yield 0.38g (73%), m.pt. 152° C.
^{1}H NMR ($CDCl_3$):
ppm: 0.97 (t, J=6.1 Hz, 6H), 1.1-2.0 (m, 8H), 4.11 (t, J=7Hz, 4H), 13.1 (br., exchanges with D_2O, 1H).

Example 16

1,3-Di-n-butyl-8-bromo xanthine

1,3-Di-n-butyl-8-bromo xanthine was prepared from 1,3-di-n-butyl-8-nitro xanthine (0.5g, 0.0016mol) and concentrated hydrobromic acid (8ml) using the procedure as described in Example 15. The title product was obtained after recrystallisation from ethanol, yield 0.4g (91%), m.pt. 178° C.
^{1}H NMR ($CDCl_3$):
ppm: 0.97 (t1 J=6.1Hz, 6H), 1.1-2.0 (m, 8H), 4.11 (t, J=6.9Hz, 4H), 13.3 (br. exchanges with D_2O, 1H).

Example 17

1,3-Di-cyclopropylmethyl-8-chloro xanthine

1,3-Di-cyclopropylmethyl-8-nitro xanthine (6g, 0.023mol) was dissolved in dimethylformamide (20ml) and r acted with phosporous oxychloride (14g) for 1 hour at 120° C. The mixture was then treated with water and stirred for 1 hour at room temperature. The precipitate was filtered off, dissolved in ethyl acetate, dried over anhydrous sodium sulphate and the solv nt was removed in vacuo, yield 2.5g (40%), m.pt. 220° C.

1.3-Di-cyclopropylmethyl-8-pyrrolidinyl xanthine

The title compound was prepared from 1,3-di-cyclopropylmethyl-8-chloro xanthine (0.3g, 0.0011mol) and pyrrolidine (0.2g, 0.0028mol) using an analogous procedure to that described in Example 19. The title product was obtained as a crystalline solid, m.pt. >250° C.
^{1}H NMR ($CDCl_3$):
ppm: 0.3-065 (m, 8H), 1.1-1.8 (m, 2H), 1.9-2.2 (m, 4H), 3.5-3.8 (m, 4H), 3.8-4.1 (m, 4H) 10.6 (br. exchanges with D_2O, 1H).

Example 23

1,3-Di-cyclopropylmethyl-8-piperidinyl xanthine

The title compound was prepared from 1,3-di-cyclopropylmethyl-8-bromo xanthine (1.2g, 0.0037mol) and piperidine (0.79g, 0.009mol) using an analogous procedure to that described in Example 19. The title product was obtained as a crystalline solid, m.pt. >250° C.
^{1}H NMR ($CDCl_3$):
ppm: 0.3-0.6 (m, 8H), 1.05-1.55 (m, 2H), 1.55-1.9, (m, 6H), 3.45-3.8 (m, 4H), 3.8-4.05 (m, 4H), 13.3 (br., exchanges with D_2O, 1H).

Example 24

1,3-Di-cyclohexylmethyl-8-piperidinyl xanthine

The title compound was prepared from 1,3-di-cyclohexylmethyl-8-bromo xanthine (0.7g, 0.0017mol) and piperidine (0.28g, 0.003mol) using an analogous procedure to that described in Example 19. The title product was obtained as a crystalline solid, m.pt. 266° C.
^{1}H NMR ($CDCl_3$):
ppm: 0.75-2.2 (m, 28H), 3.5-3.75 (m,4H), 3.75-4.05 (m, 4H), 10.72 (br. exchanges with D_2O, 1H).

Example 25

1,3-Di-cyclohexylmethyl-8-bromo xanthine

The title compound was prepared from 1,3-di-cyclohexylmethyl-8-nitro xanthine (1g, 0.0026mol) and concentrated hydrobromic acid (40ml, 48%) over 32 hours using an analogous procedure to that described in Example 15. The title product was obtained as a crystalline solid, m.pt. 247° C.
^{1}H NMR ($CDCl_3$):
ppm: 0.75-2.2 (m, 22H), 3.89 (d, J=7.2Hz, 4H), 13.45 (br. exchanges with D_2O, 1H).

Example 26

1,3-Di-cyclohexyl-8-nitro xanthine

The title compound was prepared from 1,3-di-cyclohexyl xanthine (1.5g, 0.0044mol) concentrated nitric acid (0.56g) and acetic acid (1.9ml) using an analogous procedure to that described in Example 1. The title product was obtained as a crystalline solid, m.pt. >250° C.
^{1}H NMR ($CDCl_3$):
ppm: 0.8-2.7 (m, 20H), 4-5 (m, 2H).

1,3-Di-cyclopropylmethyl-6-aminouracil

1,3-Di-cyclopropylmethyl-6-aminouracil was prepared using an analogous procedure to that described in J. Org. Chem. 16, 1879-1890, (1951):

22.6g (0.138mol) of the N,N′-dicyclopropylmethyl-urea (from Preparation 1) was treated with 44ml (0.43mol) of acetic anhydride and 14g (0.165mol) of cyanocetic-acid at 70° C for 2 hours.

After cooling and the addition of 15ml of water, 40ml of 50% NaOH/water-solution was dropped slowly onto the mixture at 45° C with stirring.

After stirring for 1 hour at room temperature, the strongly alkaline solution was separated and the oily residue washed carefully with 60ml water.

The semi-solid residue was dissolved in 220ml methanol and dropped into 1 litre of water with stirring. Thereby the product crystallised. Yield: 25.5g, 78.5% approx., m.p. 85-95° C (wax-like).

Preparation 6

1,3-Di-cyclopentylmethyl-6-aminouracil

1,3-Di-cyclopentylmethyl-6-aminouracil was prepared from N,N′-di-cyclopentylmethyl urea using a procedure analogous to that described in Preparation 5. The title compound was isolated as a crystalline solid, m.p. 108° C.

^{1}H NMR ($CDCl_3$):

ppm: 1.0-2.6 (18H, m); 3.86 (4H, d, J = 7.4Hz); 4.98 (3H, m, 2H exch. with D_2O).

Preparation 7

1,3-Di-cyclohexylmethyl-6-aminouracil

1,3-Di-cyclohexylmethyl-6-aminouracil was prepared from N,N′-di-cyclohexylmethyl urea using a procedure analogous to that described in Preparation 5. The title compound was isolated as a crystalline solid, m.p. 185° C.

Preparation 8

N,N′-Di-cyclopropylmethyl urea

N,N′-Di-cyclopropylmethyl urea, m.p. 124° C, was prepared using a procedure analogous to that described in J. Org. Chem. 16, 1879-1890, (1951):

68.2g (0.634mol) cyclopropylmethylamine-hydrochloride in 800ml of water was treated with 25g sodium hydroxide dissolved in 100ml of water and the mixture cooled to -15° C.

Phosgene, 33g was then slowly introduced through a capillary tube with stirring. Thereafter the mixture was stirred for 1 hour and, as necessary, after acidification with 0.1 N HCl, the product was extracted with dichloromethane.

After washing with water and drying over anhydrous sodium sulphate the product was obtained after evaporation of the solvent. Yield: 21g, 40% approx.

From the aqueous phase, 20g of the unreacted aduct (cyclopropylmethylamine-hydrochloride) can be obtained.

^{1}H NMR ($CDCl_3$):

ppm: 0.06-0.59 (8H, m); 0.72-1.06 (2H, m); 3.01-3.09 (4H, d); 4.66 (1H, br.s, exch. with D_2O).

Preparation 9

Results	
Example 1 No.	Ki [μM] c-AMP phosphodiesterase (erythrocytes)
1	17
2	15.9
3	6.1
4	4.8
5	5.4
7	1.3
9	1.6
10	0.53
11	0.57
13	14
17	15.1
18	23
19	<100
20	11.5
22	29.7
23	55.9
25	7.9

b) Induction of blood eosinophilia and the effects of drugs.

Animals

Male Charles River Sprague Dawley rats weighing between 250 to 300g were used.

The method used was a modification of that described by Laycock et al (Int. Arch. Appl. Immunol, (1986). 81, 363).

Sephadex G200, particle size 40 to 120 micron, was suspended in isotonic saline at 0.5mg/ml, and stored for 48h at 4° C. 1ml of the suspension was given intravenously to rats on days 0,2 and 5. A control group received saline. The test compound was given before the Sephadex on each occasion, with a contact time expected to give maximum activity at the time of the Sephadex administration. Blood was taken from the tail vein of the rats on day 7 for the determination of total and differential leucocyte counts.

A control group of at least 6 animals was included each time a compound was evaluated. The control group received Sephadex and the vehicle without test compound. The results in the drug treated animals were compared with the control group. Alternatively, if the mean for the control group for any experiment was not statistically different from the mean of the sum of all of the control groups, then the treated animal results for that experiment were compared with the mean of the sum of all the control groups.

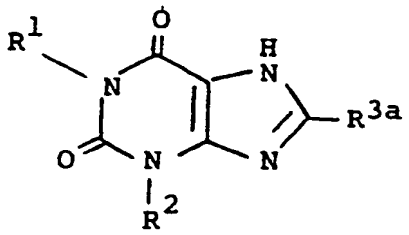
Total and differential leucocyte counts.

20μl samples of blood, taken from the tail vein of the rats, were added to 10ml of Isoton II and, within 30min, Zaponin (3 drops) was added, to lyse the erythrocytes. Five minutes later the total cell count was determined using a Coulter Counter Model DN. Differential leucocyte counts were carried out by fixing and staining a blood smear on a microscopic slide with May-Grunwald and Giemsa stains. A minimum of 400 cells were counted on each slide.

Statistics

2. A pharmaceutical composition comprising a compound of formula (I), or if appropriate a pharmaceutically acceptable salt thereof, providing that in the compound of formula (I) when R^1 and R^2 both represent methyl then R^3 is not a nitro group and a pharmaceutically acceptable carrier therefor.

3. A compound of formula (IA):



(IA)

or if appropriate a pharmaceutically acceptable salt thereof,
characterised in that:
R^1 and R^2 each independently represent alkyl or a moiety of formula (a):

$-(CH_2)_m-A$ (a)

wherein m represents zero or an integer 1, 2 or 3, A represents a substituted or unsubstituted cyclic hydrocarbon radical, providing that when R^1 represents methyl then R^2 is not methyl; and
R^{3a} represents a halogen atom, a nitro group, or a group $-NR^4R^5$ wherein R^4 and R^5 each independently represent hydrogen, alkyl or alkylcarbonyl or R^4 and R^5 together with the nitrogen to which they are attached forming an optionally substituted heterocyclic group.

4. A compound according to claim 3, wherein R^1 represents a moiety of formula (a).

5. A compound according to claim 3 or claim 4, wherein R^2 represents a moiety of formula (a).

6. A compound according to any one of claims 3 to 5, wherein R^1 and R^2 each independently represent a moiety of formula (a).

7. A compound according to any one of claims 3 to 6, wherein A represents a substituted or unsubstituted C_{3-8} cycloalkyl group.

8. A compound according to any one of claims 3 to 7, wherein A represents a substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

9. A compound according to any one of claims 3 to 8, wherein A represents a cyclopropyl group or a cyclobutyl group.

10. A compound according to any one of claims 3 to 9, wherein A represents a cyclopropyl group.

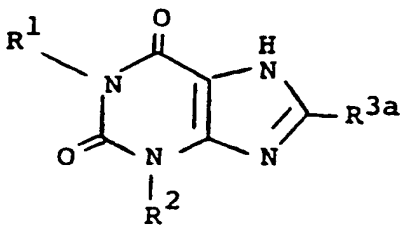
11. A compound according to any one of claims 3 to 10, wherein R^{3a} is a nitro group or a group $-NHR^4$ wherein R^4 represents hydrogen or alkylcarbonyl.

12. A compound according to any one of claims 3 to 11, wherein R^{3a} represents an amino group.

13. A compound according to any one of claims 3 to 10, wherein R^{3a} represents a halogen atom.

14. A compound according to any one of claims 3 to 10, wherein R^{3a} represents a pyrrolidinyl, piperidinyl or morpholinyl group.

15. A compound according to claim 3 selected from the group consisting of:
1,3-di-n-butyl-8-nitro xanthine;
1,3-di-cyclopropylmethyl-8-nitro xanthine;
1,3-di-cyclobutylmethyl-8-nitro xanthine;
1,3-di-cyclopentylmethyl-8-nitro xanthine;
1,3-di-cyclohexylmethyl-8-nitro xanthine;
1,3-di-n-butyl-8-amino xanthine;
1,3-di-cyclopropylmethyl-8-amino xanthine;
1,3-dicyclobutylmethyl-8-amino xanthine;
1,3-di-cyclopentylmethyl-8-amino xanthine;
1,3-di-cyclohexylmethyl-8-amino xanthine;
1,3-di-cyclopropyl-8-amino xanthine;
1,3-di-n-butyl-8-acetamido xanthine;
1,3-di-n-butyl-8-chloro xanthine;
1,3-di-n-butyl-8-bromo xanthine;
1,3-di-cyclopropylmethyl-8-chloro xanthine;
1,3-di-cyclohexyl-8-chloro xanthine;



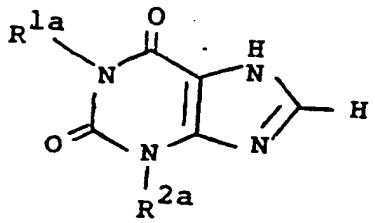
(IA)

or if appropriate a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 each independently represent alkyl or a moiety of formula (a):

$-(CH_2)_m-A$ (a)

wherein m represents zero or an integer 1, 2 or 3, A represents a substituted or unsubstituted cyclic hydrocarbon radical, providing that when R^1 represents methyl then R^2 is not methyl; and

R^{3a} represents a halogen atom, a nitro group, or a group $-NR^4R^5$ wherein R^4 and R^5 each independently represent hydrogen, alkyl or alkylcarbonyl or R^4 and R^5 together with the nitrogen to which they are attached forming an optionally substituted heterocyclic group; which process comprises reacting a compound of formula (II):



(II)

wherein R^{1a} represents R^1, as defined in relation to formula (IA), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (IA), or a group convertible thereto, with a reagent capable of substituting the C-8 hydrogen of the compound of formula (II) with a group R^{3b} wherein R^{3b} represents R^{3a}, as defined above in relation to formula (IA), or a group convertible thereto; and thereafter, if required carrying out one or more of the following optional steps:

(i) converting any group R^{1a} to R^1 and/or R^{2a} to R^2;

(ii) when R^{3b} is not R^{3a}, converting R^{3b} to R^{3a};

(iii) converting a compound of formula (IA) into a further compound of formula (IA);

(iv) converting a compound of formula (IA) into a pharmaceutically acceptable salt.

2. A process according to claim 1, for preparing a compound wherein R^1 represents a moiety of formula (a).

3. A process according to claim 1 or claim 2, for preparing a compound wherein R^2 represents a moiety of formula (a).

4. A process according to any one of claims 1 to 3, for preparing a compound wherein R^1 and R^2 each independently represent a moiety of formula (a).

5. A process according to any one of claims 1 to 4, for preparing a compound wherein A represents a substituted or unsubstituted C_{3-8} cycloalkyl group.

6. A process according to any one of claims 1 to 5, for preparing a compound wherein A represents a substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

7. A process according to any one of claims 1 to 6, for preparing a compound wherein A represents a cyclopropyl group or a cyclobutyl group.

8. A process according to any one of claims 1 to 7, for preparing a compound wherein A represents a cyclopropyl group.

9. A process according to any one of claims 1 to 8, for preparing a compound wherein R^{3a} is a nitro group or a group $-NHR^4$ wherein R^4 represents hydrogen or alkylcarbonyl.

10. A process according to any one of claims 1 to 9, for preparing a compound wherein R^{3a} represents

a limited period of time. It was up to each Contracting State to enact appropriate legislation if the State wanted such technical knowledge only to be used under limited conditions; (ii) in this case, three different interests were involved and required balancing: there was the basic interest of mankind to remedy widespread and dangerous diseases, on the other hand the environment had to be protected against the uncontrolled dissemination of unwanted genes and, moreover, cruelty to animals had to be avoided; and (iii) the provision of a type of test animal useful in cancer research and giving a rise to a reduction in the amount of testing on animals together with a low risk connected with the handling of the animals by qualified staff could generally be regarded as beneficial to mankind. The Examining Division stressed that the above considerations applied solely to this case and that other cases of transgenic animals might be excluded by A53(a).

T12/90
BAYER
Skilled person to determine extent of A54(3) citation
[1991] 5 EPOR 312

In an appeal from a decision of the Examining Division to refuse the application for lack of novelty under A54 made on the basis that, when read by the skilled person, an earlier patent application citable under A54(3) anticipated the claims even though the text of the earlier application did not specifically disclose the elements of the main claim in question, the TBA stated (i) that the novelty of an invention whose subject matter is a choice among a known group depends on whether the choice adduces a teaching of a technical nature not contained in the state of the art; and (ii) the disclosure in a prior document likely to affect the novelty of a claim is not necessarily limited to the specific examples but comprises any reproducible technical teaching

described in the document. The TBA accepted the application on the basis of an auxiliary set of claims.

Refs: T2/81 (OJ EPO 10/1982,394) and T124/87 (p.298) followed.

NOTE: In T233/90 (Special Edition OJ EPO 1993,18) it was held that where an A54(3) document referred to "a usual manner" of preparing a product, it was permissible to use reference documents such as textbooks, encyclopaedia and dictionaries to determine what the skilled person would understand from such a disclosure. See also T167/84 (p.349).

T3/90
BT/Indication of non-attendance deemed withdrawal of request for hearing
OJ EPO 12/1992,737

Following a decision by the Opposition Division to reject an opposition against the patent, the opponent appealed. Both parties requested oral proceedings on an auxiliary basis. In a summons to oral proceedings, the TBA indicated that it might disregard some late filed evidence. The opponent contested the opinion in writing and indicated that it would not be attending oral proceedings. In response, the TBA cancelled the oral proceedings, stating that according to Board of Appeal practice, a request for oral proceedings on an auxiliary basis was to be regarded as a request for oral proceedings unless the Board intended to decide the case in favour of the requesting party. The opponent's statement that it would not be attending oral proceedings was to be regarded as a withdrawal of its request for oral proceedings on an auxiliary basis, so in this case the scheduled oral proceedings could be cancelled.

NOTE: In T35/92 (not published) it was held that a failure to reply to a communication from the EPO asking whether a request for oral proceedings, made